AMENDMENTS TO THE SPECIFICATION

➢ Please amend the specification by inserting the following header and paragraph as the first paragraph of the specification immediately after the title:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a national stage filing under 35 U.S.C. 371 of International Application PCT/US/98/10909, filed May 29, 1998, which is a continuation of U.S. App. No. 08/866,827, now abandoned, which claims the benefit of U.S. Provisional Application Nos. 60/048,062 and 60/048,063, filed May 30, 1997, the specifications of each of which are incorporated by reference herein in its entirety.

➢ Please amend the three paragraghs starting from page 9, lines 6 - 17 as below:

Figure 1A-1C is a graph showing bone forming activity induced by systemic OP-1 administration. Bovine collagen carrier (25 mg) was implanted at subcutaneous sites (open bar) and intramuscular sites (filled bar). OP-1 was administered via the tail vein (500 ug x 5 times, 50 ug x 1, 500 ug x 1, or 2500 ug x 1). Panel 1A shows the amount of alkaline phosphatase induced, Panel 1B shows the calcium content of the implant, and Panel 1C shows the histologic examination of the implants harvested at 12 days after implantation. See Example 4 for experimental details.

Figure 2A-2C is a graph showing the effect of timing of OP-1 administration on bone forming activity. Bovine collagen carrier (25 mg) was implanted at ~~intramuscular and~~ subcutaneous sites (open bar) and intramuscular sites (filled bar), and OP-1 was administered via the tail vein (1500 ug as a single injection) 1, 3, 5, 7, or 9 days after collagen implantation. Bone forming activity was determined by histology (Panel 2C), the amount of alkaline phophatase induced (Panel 2A), and calcium content of the implant (Panel 2B) at 12 days after administration of OP-1. See Example 3 for experimental details.

Figures 3A ~~and~~ -3B shows the effect of the age of an animal on bone-forming activity induced by systemical ly-administered OP-1 Bovine collagen carrier (25 mg) was implanted at

subuctaneous~~ly~~ sites (open bar) and intramuscular~~ly~~ sites (filled bar). OP-1 was administered via the tail vein (2500 ug as a single injection) 24 hours after carrier implantation. Bone-forming activity was determined by alkaline phosphatase activity (~~Figure~~ Panel 3A), calcium content (~~Figure~~ Panel 3B), and by histology conducted on implants at 12 days after OP-1 implantation. See Example 7 for experimental details.

➢ Please amend the paragraph starting at page 44, line 15 as below:

Osteogenesis induced by OP-1 (2.5 mg/rat), as measured by determined bythe amount of alkaline phophatase induced (Panel 2A), calcium content of the implant (Panel 2B), and histology (Panel 2C) was maximal when OP-1 was administered 24 or 72 hours after collagen implantation. An approximately 30% reduction in osteogenesis was observed when OP-1 was administered 6 hours after implantation. Figure 2A-2C shows these results for implants at subcutaneous sites (open bar) or intramuscular sites (filled bar). In each case, OP-1 was administered at the time point indicated, and osteogenesis was measured at day 12 after OP-1 administration. At times longer than 120 hours (i.e. 5 days) post-implantation OP-1 failed to induce bone, suggesting that collagen may have already been committed to fibroblast lineages, and therefore non-responsive to OP-1.

➢ Please amend the paragraph starting at page 48, line 13 as below:

A comparison of OP-1 effects with related members of the morphogen family shows that OP-1 is more potent than BMP-2, CDMP-1 (GDF-5), and CDMP-2 (GDF-6) in inducing osteogenesis upon systemic administration as measured by calcium content and histology performed on day 12 implants.

The effect on osteogenesis at local collagen implant sites in animals given OP-1 systemically was independent of age. ~~Resulst~~ Results are shown in Figures 3A ~~and~~ 3B. The effect of OP-1 was determined on 24-month old, i.e., adult, rats (left set of bars) and on 1-month old, i.e., juvenile, rats (right set of bars), which received collagen implants at subcutaneous sites (open bar) or intramuscular sites (filled bars). The bone-forming activity was determined by alkaline phosphatase activity (Panel 3A) and by calcium content (Panel 3B). As shown in ~~Figure~~

Panel 3B there was some delay in the rate of bone remodeling and mineralization as determined by calcium content.